HFA-305

JUL 11 2003

Approval Date: _____

FREEDOM OF INFORMATION SUMMARY

New Animal Drug Application

NADA 141-215

EQUIMAX™ (ivermectin 1.87%/praziquantel 14.03%) Paste

EQUIMAX Paste is a broad spectrum anthelmintic and boticide for use in horses. The paste is a combination of ivermectin (dosed at 200 mcg/kg of bodyweight) and praziquantel (dosed at 1.5 mg/kg bodyweight).

Sponsor:

Virbac AH, Inc.
3200 Meacham Blvd.
Fort Worth, TX 76137

NADA 141-215 FOIS

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-215
b.	Sponsor:	Virbac AH, Inc. 3200 Meacham Blvd. Fort Worth, TX 76137 Drug Labeler Code: 051311
c.	Established Name:	Ivermectin/Praziquantel Paste
d.	Proprietary Name:	EQUIMAX™ Paste
e.	Dosage Form:	Oral Paste
f.	How Supplied:	EQUIMAX™ Paste is supplied in 0.225 oz (6.42 g) syringes. Each syringe contains sufficient paste to treat one 1320-lb horse at the recommended dose rate. Each weight marking on the syringe plunger delivers enough paste to treat 220 lb (100 kg) of body weight.
g.	How Dispensed:	OTC
h.	Amount of Active Ingredients:	Each milligram of EQUIMAX Paste contains 0.0187 milligram (1.87%) ivermectin and 0.1403 milligram (14.03%) praziquantel. Each syringe contains 120.1 mg of ivermectin and 897.6 mg praziquantel.
i.	Route of Administration:	Oral
j.	Species/Class:	Equine
k.	Recommended Dose:	The recommended dose for oral administration of EQUIMAX™ Paste is 91 mcg ivermectin per pound (200 mcg/kg) and 0.68 mg praziquantel per pound (1.5 mg/kg) of body weight.
l.	Pharmacological Category:	Anthelmintic and boticide

m. Indications: Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism. EQUIMAX™ (ivermectin/praziquantel) Paste is indicated for the treatment and control of the following parasites:

- Tapeworms: *Anoplocephala perfoliata*
- Large Strongyles (adults): *Strongylus vulgaris* (also early forms in blood vessels), S. *edentatus* (also tissue stages), *S. equinus*, *Triodontophorus* spp.
- Small Strongyles including those resistant to some benzimidazole class compounds (adults and fourth-stage larvae): *Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp.
- Pinworms (adults and fourth-stage larvae): *Oxyuris equi*
- Ascarids (adults and third- and fourth-stage larvae): *Parascaris equorum*
- Hairworms (adults): *Trichostrongylus axei*
- Large-mouth Stomach Worms (adults): *Habronema muscae*
- Bots (oral and gastric stages): *Gasterophilus* spp.
- Lungworms (adults and fourth-stage larvae): *Dictyocaulus arnfieldi*
- Intestinal Threadworms (adults): *Strongyloides westeri*
- Summer sores caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae.
- Dermatitis caused by Neck threadworm microfilariae, *Onchocerca* sp.

2. EFFECTIVENESS:

a. Dosage Characterization

The 200 mcg/kg dose for ivermectin was selected based on approval of the sponsor's ANADA 200-320 for EQUELL™ Paste (ivermectin 1.87%), dated August 9, 2002. A non-interference study (summarized below) demonstrates that the presence of praziquantel does not affect the effectiveness of ivermectin.

The praziquantel dose (1.5 mg/kg) was selected based on studies reported in the scientific literature that demonstrate that the optimal dose of praziquantel to reach at least 95% effectiveness against *A. perfoliata* infection is ≥ 1.0 mg/kg, irrespective of the method of assessment.[1-4] Doses of 0.5 mg/kg (85% effectiveness, n=24) and 0.25 mg/kg (35% effectiveness, n=36) appeared to be insufficient.

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1 Lyons E.T. *et al;* Activity of Praziquantel against *Anoplocephala perfoliata* (Cestoda) in horses, J. Helminthol. Soc. Wash. (1992), 59, 1-4.

2 Lyons E.T. *et al;* Activity of Praziquantel (0.5 mg/kg) against *Anoplocephala perfoliata* (Cestoda) in equids, Vet. Parasitol. (1995), 56, 255-257.

3 Lyons E.T. *et al;* Efficacy of Praziquantel (0.25 mg/kg) on the cecal tapeworm (*Anoplocephala perfoliata*) in horses, Vet. Parasitol. (1998), 78, 287-289.

4 Slocombe J.O.D.; The critical test for *Anoplocephala perfoliata* in equids and efficacy of B1995 oral paste for the parasite; In: Penzhorn, B.L., Krecek, R.C. (Eds.), World Assoc. Adv. Vet. Parasit. Sixteenth International Conference, Sun City, South Africa, August 10-15, 1997, Abst. No. 299, 78.

The combination product containing 1.87% ivermectin and 14.03% praziquantel was also tested in dose determination studies and dose confirmation studies conducted in Argentina and Brazil. The two dose determination studies resulted in 91% (n=6) and 97% (n=6) effectiveness for the 1.5 mg/kg dose of praziquantel, with no statistical difference when the dose was increased to 3.0 mg/kg. The two dose confirmation studies resulted in 97% (n=15) and 100% (n=6) effectiveness for the 1.5 mg/kg dose.

b. Substantial Evidence: A dose confirmation study and a non-interference study were conducted in the U.S. to provide substantial evidence of effectiveness:

Dose confirmation study of 1.5 mg praziquantel per kg body weight in the treatment of natural infection with *Anoplocephala perfoliata* in horses.

(1) Type of Study: Dose Confirmation Study

(2) Investigator: Craig R. Reinemeyer, DVM, PhD
East Tennessee Clinical Research, Inc.
Knoxville, Tennessee 37909

(3) Study Design: Critical study design, each horse served as its own control, all horses were treated with investigational drug

(a) Purpose: To confirm the effectiveness of ivermectin/praziquantel paste administered orally at 1.5 mg/kg body weight against *A. perfoliata* infections of horses.

(b) Test Animals: Twelve adult horses (4 mares, 3 stallions and 5 geldings) weighing 166 to 435 kilograms were enrolled in the study.

(c) Control Group: Each horse served as its own control.

(d) Diagnosis: The horses were confirmed to be infected with *Anoplocephala* spp. based on fecal examination prior to enrollment in the study. The horses were otherwise healthy.

(e) Dosage Form: A laboratory batch of praziquantel paste was used as the test article. The batch contained 14.03% praziquantel w/w in a formulation similar to EQUIMAX, which contains 1.87% ivermectin and 14.03% praziquantel.

(f) Route of Administration: Oral

(g) Dose: 1.5 mg praziquantel per kilogram of body weight

(h) Test Duration: March 2000 through July 2000

(i) Pertinent Variables Measured:

1 General health examinations – General health examinations were conducted through Day 10 of the study and observations recorded.

2 Fecal examinations/worm counts – The total fecal output of each horse was examined for expelled *A. perfoliata* for 10 days after treatment with the test article. On Day 10 of the study, the horses were necropsied. The mucosa of the small intestine, cecum, and large intestine of each horse was examined for attached *A. perfoliata* or scolices and the intestinal contents were washed over sieves and examined for retained *A. perfoliata*.

(4) Results:

(a) Health and Clinical Examinations – No abnormal findings in test subjects were noted in any of the horses.

(b) Fecal examination/worm counts – The twelve horses expelled 43 *A. perfoliata* in the feces in ten days after treatment (Table 1). No *A. perfoliata* were found attached to the gut mucosa and none were recovered from the gut contents of any horse post-mortem.

Table 1.

Horse #	Sex	Wt.	Dose of PZQ (mg)	*A. perfoliata* found in Day -1 feces	*A. perfoliata* expelled after treatment (Days 0-10)	Remaining *A. perfoliata* at necropsy
117	Ma	336	504	0	11	0
124	G	166	249	0	2	0
131	St	391	586.5	0	16	0
133	G	248	372	0	3	0
222	G	321	481.5	0	4	0
228	G	343	514.5	0	1	0
197	Ma	418	627	0	2	0
198	Ma	435	652.5	0	1	0
224	Ma	322	483	0	0	0
226	St.	326	489	0	3	0
234	G	389	583.5	0	1	0
241	St	409	613.5	0	0	0

Ma = Mare, St = Stallion, G= Gelding, PZQ = Praziquantel

(5) Statistical Analysis:

The product was 100% effective against *A. perfoliata* infections as evidenced by the lack of worms at necropsy of the horses; therefore, no statistical analysis was necessary.

(6) Conclusions:

Praziquantel paste administered at a rate of 1.5 mg/kg body weight to horses was 100% effective in eliminating *A. perfoliata* infections.

(7) Adverse Reactions:

No adverse reactions to the test product were noted during this study.

Non-interference study of praziquantel and ivermectin in the treatment of natural infection with *A. perfoliata* and gastrointestinal nematodes in ponies.

(1) Type of Study: Non-Interference Study

(2) Investigator(s): Thomas R. Klei, PhD
Louisiana State University Agricultural Center
Baton Rouge, Louisiana 70803

(3) Study Design: Controlled study design

(a) Purpose: To determine whether the combination of praziquantel (1.5 mg/kg dose) and ivermectin (200 mcg/kg dose) in the same formulation would interfere with the effectiveness of either compound when administered alone.

(b) Test Animals: Thirty-two ponies (6 males and 26 females) weighing 154 to 330 kilograms were enrolled in the study and randomly assigned to 4 groups containing 8 ponies each.

(c) Control Group: A placebo-treated control group was included in the study.

(d) Diagnosis: The ponies were confirmed to be infected with *Anoplocephala* spp. and nematodes based on fecal examination prior to enrollment in the study. The ponies were otherwise noted to be healthy.

(e) Dosage Form: The test articles were oral pastes. Pastes included Placebo Paste (excipients only), 14.03% Praziquantel Paste, 1.87% Ivermectin Paste and 14.03% Praziquantel/1.87% Ivermectin Paste.

(f) Route of Administration: Oral

(g) Dose(s):

- Control - 0 mg ivermectin and 0 mg praziquantel
- 1.5 mg praziquantel per kilogram of body weight
- 200 mcg ivermectin per kilogram of body weight
- 1.5 mg praziquantel and 200 mcg ivermectin per kg of body weight

(h) Test Duration: April 2000 through August 2000

(i) Pertinent Variables Measured:

1 General health examinations – General health examinations were conducted until completion of the study and observations were recorded.

2 Fecal examinations/worm counts – Fecal egg counts were obtained 14 days post treatment in addition to worm counts at necropsy. On Days 14-17 of the study, the ponies were necropsied; eight ponies were necropsied each day. The mucosa of the small intestine, cecum, and large intestine of each horse was examined for attached *A. perfoliata* or scolices, and 5% of the cecum and large colon contents were collected and processed to count small strongyle adults and nematode larvae. The remaining intestinal (small and large intestine) contents were washed over sieves and examined for retained *A. perfoliata*, large strongyles and other nematodes. Samples of the large intestine wall were obtained and processed following standard transillumination and digestion techniques to examine encysted larvae of small strongyles. The cranial mesenteric artery and its branches were also dissected for recovery of migrating *Strongylus vulgaris* larvae.

(4) Results:

(a) Health and Clinical Examinations – No abnormal findings were noted in any of the ponies.

(b) Fecal Examination/Worm Counts – Fecal counts made prior to treatment indicated that *Anoplocephala* spp. and strongyle spp. were present in all ponies.

Feces obtained 14 days post treatment were negative for proglottids. Additionally, fecal egg counts 14 days post treatment demonstrated a 100% removal of strongyle eggs in the two groups treated with ivermectin and a 100% removal of *Anoplocephala* eggs in the two groups treated with praziquantel (Table 1).

Necropsy data demonstrated that ivermectin, either alone or in combination with praziquantel, was highly effective (99.9 to 100%) against *Gasterophilus intestinalis* 3rd instars, *Strongylus edentatus* adults, luminal cyathostomes 4th stage larvae and adult cyathostomes (Table 2) when compared to the untreated control group. Ivermectin had no effect on mucosal cyathostomes detected by digestion.

Praziquantel, either alone or in combination with ivermectin, significantly (100%) reduced the numbers of *A. perfoliata* found in the large intestine (Table 2) when compared to the untreated control group. Praziquantel had no effect on nematode parasites or *Gasterophilus* larvae, except where noted in Table 2.

Table 2. Arithmetic mean strongyle (N) fecal egg counts and the presence or absence of *Anoplocephala* (A) spp. eggs prior to treatment and on Day 14

	TREATMENT GROUPS							
	1 (IVM†)		2 (PZQ‡)		3 (IVM + PZQ)		4 (CONTROL)	
	N	A	N	A	N	A	N	A
Pre-treatment	428* 8/8**	8/8	491 8/8	8/8	529 8/8	8/8	453 8/8	8/8
Day 14	0 0/8	5/8	436 7/8	0/8	0 0/8	0/8	518 8/8	6/8

†IVM = Ivermectin
‡PZQ = Praziquantel
* Arithmetic means of strongyle eggs per gram of feces.
** Number of horses with eggs present/number examined.

Table 3. Geometric mean worm counts at necropsy and percent reduction as compared to untreated controls

	TREATMENT GROUPS			
	1 (IVM†)	2 (PZQ‡)	3 (IVM + PZQ)	4 (CONTROL)
Anoplocephala perfoliata	45 [a]* (0) **	0 [b] (100)	0 [b] (100)	31 [a]
Gasterophilus intestinalis 3rd Instars	0 [a] (100)	24 [b] (0)	0 [a] (100)	21 [b]
Strongylus edentatus	0 [a] (100)	0.67 [a] (83)	0 [a] (100)	3.83 [b]
Cyathostome L4	5.3 [a] (99)	2401.7 [b] (61)	7.0 [a] (99.9)	6161 [b]
Adult Cyathostome	35.1 [a] (99.9)	7308.7 [b] (71.6)	26.9 [a] (99.9)	25703.0 [b]
Mucosal Cyathosome	681.1 [a] (30.9)	2082.1 [a] (0)	700.8 [a] (28.9)	985.1 [a]

†IVM = Ivermectin

‡PZQ = Praziquantel

* For each row in table, geometric means followed by a different letter are significantly different ($p < 0.05$).

** Percent reduction computed as $100 \times (GM_4 - Gm_i)/GM_4$ (where i = Treatment groups 1,2,3 and 4 = control group).

(5) Statistical Analysis:

The statistical analysis of the data was based on a logarithmic transformation. Differences among the four treatment groups were statistically evaluated via one-way analysis of variance (ANOVA), followed by pairwise comparisons of the treatment group means based on Tukey's honestly–significant–difference (HSD) method at the 5% level of significance.

(6) Conclusions:

The combination product of ivermectin (200 mcg/kg body weight) and praziquantel (1.5 mg/kg body weight) is highly effective (99.9-100%) against luminal stages of cyathostome nematodes, large strongyles (*S. edentatus*), *G. intestinalis* 3rd instars and *A. perfoliata*. The combination of ivermectin and praziquantel did not interfere with the effectiveness of either compound when administered alone.

(7) Adverse Reactions:

No adverse reactions to the test product were noted during this study.

3. TARGET ANIMAL SAFETY:

a. Acute Toxicity and Tolerance

The safety of EQUIMAX Paste in foals 14-28 days of age was demonstrated in the study described below.

(1) Type of Study: Acute Toxicity and Tolerance

(2) Investigator(s): Larry Cruthers, PhD
Professional Laboratory Research Services
Corapeake, North Carolina 27926

(3) General Design of the Study:

(a) Compliance: This study was conducted in accordance with Good Laboratory Practices For Nonclinical Laboratory Studies, U.S. Code of Federal Regulations, Title 21, Part 58, April 1998.

(b) Purpose of Study: To determine the safety of EQUIMAX Paste in foals. Toxicity was assessed under a three-day treatment regimen of one, three or five times the recommended dose. Tolerance was determined with a single dose of ten times the recommended dose.

(c) Test Animal Allocation and Drug Administration: For the toxicity study, foals were assigned to one of four groups as follows:

Table 4.

Group	No. Animals[a]	Type	Route	Dose	Frequency	Regimen
1	6	Control	Oral	5x[b]	Single dose	Days 0,1,2
2	6	Test	Oral	1x	Single dose	Days 0,1,2
3	6	Test	Oral	3x	Single dose	Days 0,1,2
4	6	Test	Oral	5x	Single dose	Days 0,1,2

[a] Three males and three females per group
[b] Control article: 5x = an amount corresponding to the volume of test article given at five times the recommended dose of each active ingredient.
Test article: 1x, 3x, 5x = one, three, and five times the recommended dose of each active ingredient, respectively.

For the tolerance study, an additional group of foals was assigned as follows:

Table 5.

Group	No.Animals[a]	Type	Route	Dosage[b]	Frequency	Regimen
1	4	Test	Oral	10x	Single dose	Day 0

[a] Two males and two females.

[b] Test article: 10x = ten times the recommended dose of each active ingredient.

(d) Test Duration: April 2000 through September 2000

(e) Pertinent Variables Measured: Physical examinations were conducted on Days -3 to 0 & Day 16 in the toxicity study and Days -3 and 0 and 14 in the tolerance study. Clinical observations were conducted twice daily to assess general appearance, attitude, behavior and appetite. Body weights were taken in concurrence with physical examinations. Animals were observed for adverse drug events immediately following treatment for the 1st hour and then hourly through 6 hours posttreatment. Clinical pathology testing (hematology, serum biochemistry) was conducted on baseline samples for both studies on Day -7 & Day 0. Additionally, clinical pathology was performed on samples collected in the toxicity study on Days 3, 7 and 16 and in the tolerance study on Days 7 and 14. Gross postmortem examination was performed on all treatment groups in the toxicity study. Additionally, histopathology was conducted on the placebo and 5X animals. In the tolerance study, gross post mortem and histopathology were performed on all foals in the 10X group. The continuous outcomes were analyzed by a repeated measures analysis of variance and dichotomous outcomes were analyzed by the Fisher's exact test.

(4) Results:

(a) Clinical Findings: Three foals in the toxicity study had abnormal clinical findings noted during the twice-daily post-treatment clinical observations. One foal in the 1X group was observed to cough on Days 11 and 14 and to have "raspy breathing" on Day 15. One foal in the 5X group was reported to be lethargic on Day 14, with "drooping ears" on Days 14-15. The observations resolved spontaneously. One foal in the 3X group was removed from the Study on Day 4 with a clinical diagnosis of bronchopneumonia. None of the abnormal clinical findings were considered to be associated with the administration of the test article.

One foal in the (10X) tolerance study was noted to have loose watery stools during the twice-daily post-treatment clinical

observations on Days 1, 2, and 5-9. These signs resolved without treatment by Day 10, and no other 10X foals were observed to have similar signs throughout the post-treatment clinical observation period.

(b) Clinical Observations and Pathology: Dose-related effects were found in the toxicity study for trigylcerides (placebo group mean was lower than those of the active treatments, $P \leq 0.03$), direct bilirubin (placebo group mean was higher than that of the 3X, P=0.006 and 5X groups, P=0.01), and heart rate (placebo group mean was lower than that of the 5X group, $P \leq 0.007$). For these three variables there were only a few values above or below the pre-treatment ranges (set as the minimum and maximum values recorded on Days –7 and 0 since there are no published normal ranges for 2 week old foals), and none of the changes were considered clinically significant.

There were individual measurements above or below the pre-treatment range for the remaining clinical pathology tests and clinical observations. The observations were distributed among the treatment groups. For example, for creatine kinase (CK), there were ten values below the pre-treatment range (two in the placebo group, four in the 1X group, three in the 5X group and one in the tolerance study). The highest CK values were observed prior to treatment in the tolerance group. Values for prothrombin time tended to rise with time in all groups and most of the post-treatment values were outside of the range of the pre-treatment values. Activated prothrombin times far exceeded the laboratory's reference range for adult horses; however, elevated values were found in all treatment groups at all time points. Observations of clinical pathology values or clinical observations outside of the pre-treatment ranges were not clinically significant.

(c) Post-mortem Pathology: No post-mortem gross pathologic findings were observed that were associated with the administration of the test or control articles. There were no biologically significant differences in the occurrences of histopathologic changes between the placebo horses and the 5x treated horses.

(5) Conclusions:

This study demonstrated that EQUIMAX Paste is safe for use in foals 14-28 days of age. No signs of toxicity were observed when this oral paste was administered for three consecutive days at 1, 3, and 5 times the single recommended dose or as a single dose of ten times the recommended dose.

b. Target Animal Safety - Breeding Safety in Stallions

The safety of EQUIMAX Paste in stallions was demonstrated in the study described below.

(1) Type of Study: Target Animal Safety

(2) Investigator(s): Edward L. Squires, PhD
Animal Reproduction and Biotechnology Laboratory
Colorado State University
Fort Collins, Colorado 80523

(3) General Design of the Study:

(a) Compliance: This study was conducted in accordance with Good Laboratory Practices For Nonclinical Laboratory Studies, U.S. Code of Federal Regulations, Title 21, Part 58, April 1998.

(b) Purpose of Study: To evaluate the clinical and reproductive performance of stallions (based on breeding behavior, semen variables, testicular measurements, physical examinations, and hormonal concentrations) when treated with three times the recommended dose of EQUIMAX Paste on three occasions through one cycle of spermiogenesis.

(c) Test Animal Allocation and Drug Administration: Twenty-four healthy, domestic, light-breed stallions between 3-15 years of age were administered either test or control article oral paste at a volume three times the normal dose of each active ingredient for three treatments (Days 0, 7 and 14).

(d) Test Duration: May 2000 through August 2000

(e) Pertinent Variables Measured: Genital examinations and testicular measurements were conducted on Days -11, -5, 7, 13, 21, 65 and 79. Semen was collected every other day from Days -21 to 21 and again from Days 51 to 79. Semen from Days -13 to 21 and Day 61-79 was evaluated for color, consistency, ejaculate volume, spermatozoal concentration, total spermatozoa per ejaculate, morphology, motility, percentage progressively motile, velocity, longevity and daily sperm output. Breeding behavior was evaluated in conjunction with semen collections. Blood was obtained for hormone concentrations on Days -2, -1, 0, 13, 14, 15,

38, 39, 40 77, 78 and 79. Blood was obtained for hematology and clinical chemistries on Days 0, 2, 7, 9, 14, 16, 39 and 79. Body weights were measured and physical examination conducted on Days -21, -11, 0, 13, 25, 39, 50, 65 and 79. Horses were observed daily for general appearance, behavior, attitude, appetite and adverse reactions.

Observational assessment data collected included breeding behavior, physical examination variables, weight, scrotal width, scrotal volume and clinical observations. All the continuous outcome data were analyzed by repeated measures analysis of variance. Some outcomes were logarithmically transformed before a repeated measures analysis was performed; for example, time to erection. The categorical libido assessments and score semen variables were analyzed by an exact chi-square test.

(4) Results:

(a) Hematology – Segmented neutrophils were significantly higher in the treated group on Day 16 (P=0.0014; Table 6). Lymphocytes were significantly lower in the treated group on Day 16 (P=0.0002; Table 6). The significant differences in hematology values were considered to be of no clinical significance since the values fell within the expected range for mature male horses.

(b) Chemistry – Prothrombin Time and creatinine were significantly lower in the treated group on Day 2 and 79, respectively (P=0.0015 and P=0.048, respectively; Table 6). CK values were significantly greater in the treated group, regardless of time (P=0.077; Table 6). All reported differences in chemistry values appear to be of little consequence since the values were within the normal levels reported for mature male horses. Furthermore, there were few values after Day 0 outside the pretreatment range for treated stallions.

(c) Semen Quality – On Study Days 5 and 75, Gel Volume in treated stallions was significantly lower and higher, respectively, than stallions receiving placebo (P=0.058 and 0.039, respectively; Table 6). Concentration was significantly higher in the treated group versus placebo (P=0.037, Table 6). The differences between groups, though significant, were not considered to be of any biological consequence. Motility on Days 13 and 19 was improved in the treated group (P=0.069 and 0.089, respectively, Table 7).

(d) Reproductive Hormone Analysis - No statistically significant differences were found for LH levels. On Day 40, testosterone was less in the treated group compared to placebo (P=0.018). No other testosterone differences were noted throughout the study. Only one stallion, in the placebo group, had FSH levels above zero.

(e) Respirations - Respirations were significantly lower in the treated group on Day 13 (P=0.025). Differences in respiratory rate between the groups were considered to be of no biological significance.

(f) Breeding behavior - Statistically significant differences were found for restlessness (P=0.089) on Day 7, pawing (P=0.037) on Day 7 and flehmen (P=0.069) on Day 63. Restlessness and pawing were found to be more common in the treated group, but flehmen reaction was found to be more common in the control group. These differences were probably due to chance alone. Differences were small and were of no biological significance. None of these behavior variables had any effect on the ejaculatory process.

Table 6. Statistically significant findings for continuous variables.

Variable	Day	Least-Square Mean		P-Value
		Treated Group	Control Group	
Hematology				
Segmented Neutrophils	16	6.07	4.87	0.0014
Lymphocytes	16	1.57	2.65	0.0002
Serum biochemistry				
Prothrombin Time	2	11.28	12.65	0.0015
Creatine kinase	Overall	209.28	173.39	0.077
Creatinine	79	1.38	1.47	0.048
Semen				
Gel Volume	5	8.17	18.30	0.058
	75	17.25	6.22	0.039
Concentration	Overall	357.43	285.52	0.037
Physical				
Respiration	13	20.4	24.93	0.025
Hormones				
Testosterone	40	0.57	0.93	0.018

Table 7. Statistically significant findings for categorical variables.

Variable	Day	Treated Group			Control Group			P-Value
		# Improved	# Total	%	# Improved	# Total	%	
Semen								
Motility	13	11	12	91.67	6	12	50.00	0.069
	19	10	12	83.33	5	12	41.67	0.089
Breeding Behavior								
Restlessness	7	7	12	58.33	2	12	16.67	0.089
Pawing	7	5	12	41.67	0	12	0.00	0.037
Flehmen	63	1	12	8.33	6	12	50.00	0.069

(5) Conclusions:

This study demonstrated the safety of EQUIMAX Paste in breeding stallions. There were no clinically significant biological effects of treatment on hematology, blood chemistry, semen quality, breeding behavior, physical examination, testicular measurements or reproductive hormone levels (LH, testosterone, FSH).

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Not for use in humans. Keep this and all drugs out of the reach of children. Refrain from eating and smoking when handling. Wash hands after use. Avoid contact with eyes. The Material Data Safety Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Pfizer at 1-800-366-5288."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrates that EQUIMAX™ (ivermectin 1.87%/praziquantel 14.03%) Paste, when used under labeled conditions of use, is safe and effective for the treatment and control of various species of internal parasites.

EQUIMAX™ Paste is labeled for OTC use. Routine deworming of horses is a widely accepted and recommended practice performed by the lay person. A diagnosis of parasite infection prior to deworming is not necessary.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

EQUIMAX™ Paste is under the following U.S. patent number:

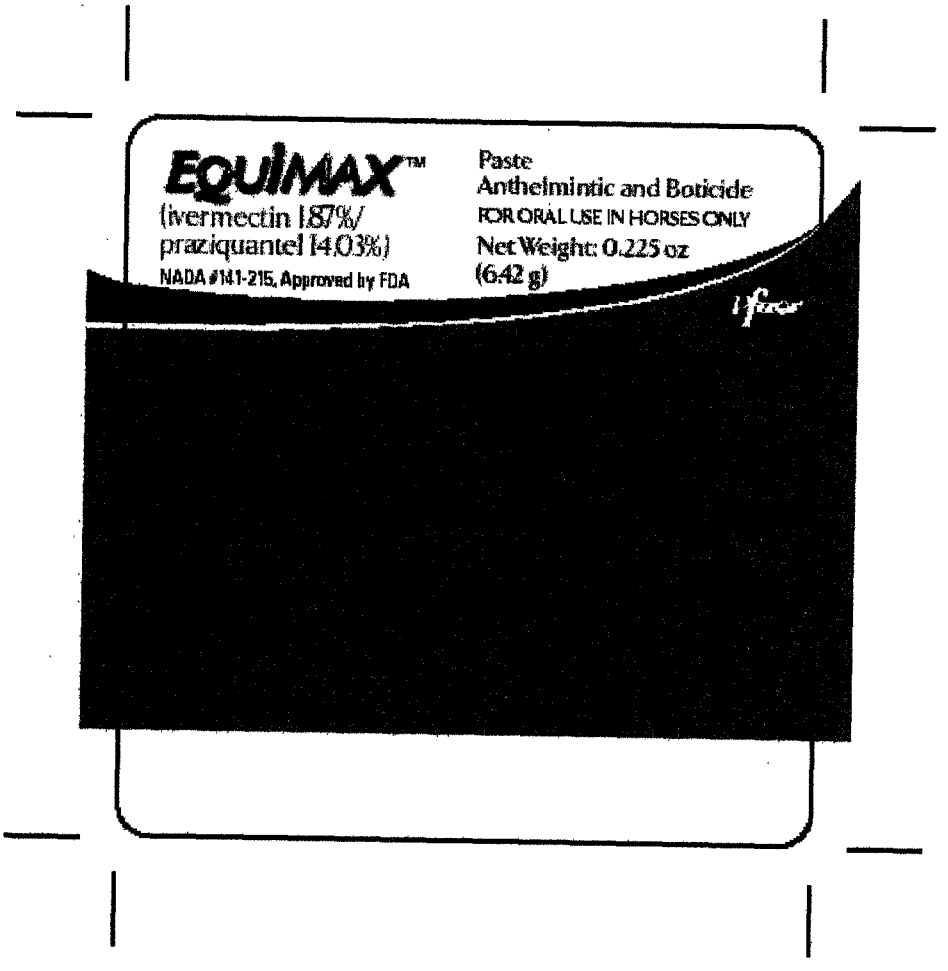
U.S. Patent Number	Date of Expiration
5,824,653	11/27/2015

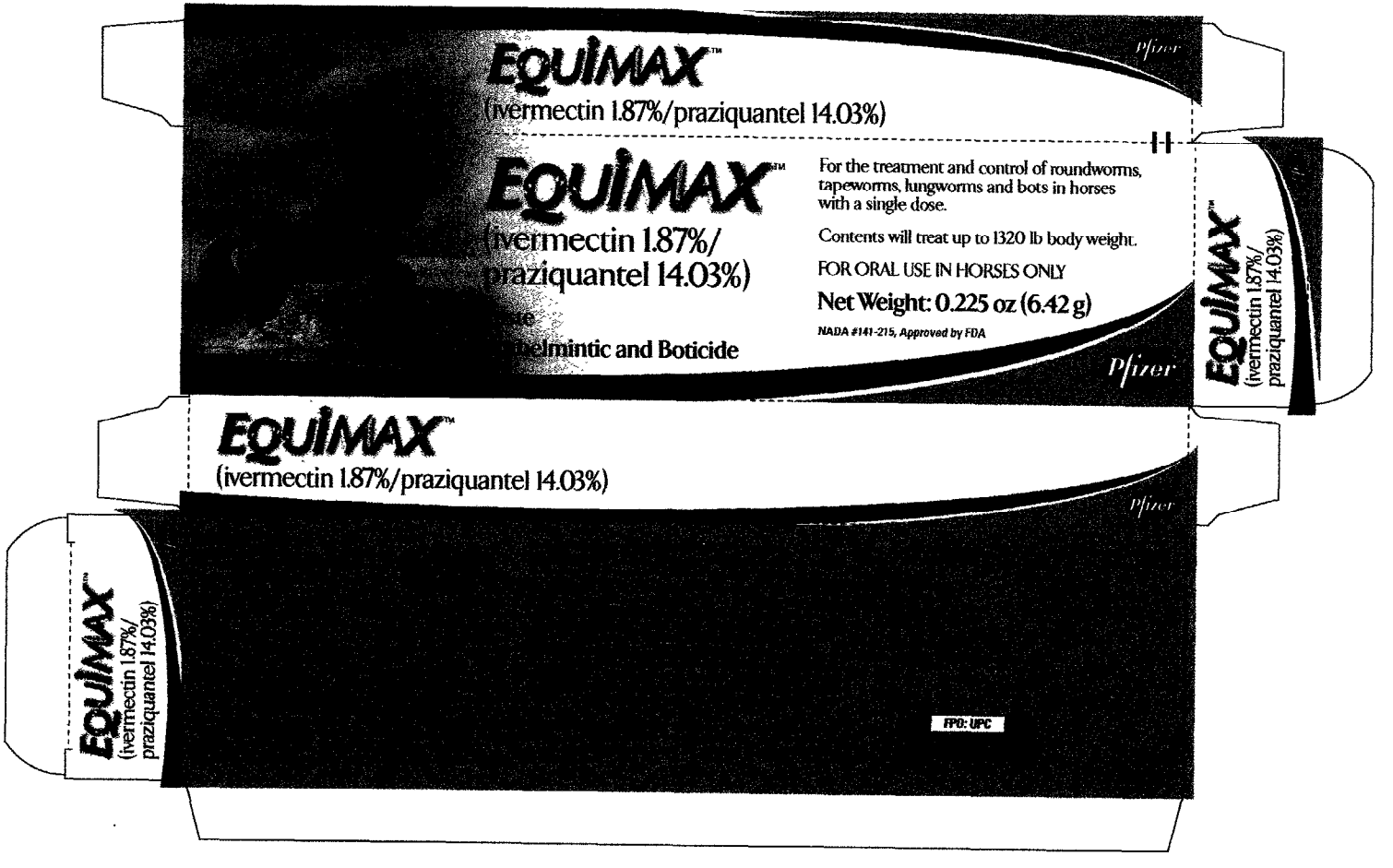
6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

a. Syringe label
b. Container Label (box containing syringe)
c. Package Insert
d. Counter Display

Enlarged


EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
NADA #141-215, Approved by FDA
Paste
Anthelmintic and Boticide
FOR ORAL USE IN HORSES ONLY
Net Weight: 0.225 oz
(6.42 g)
Pfizer


EQUIMAX™
(ivermectin 1.87%/praziquantel 14.03%)
Pfizer
EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
Delmintic and Boticide
For the treatment and control of roundworms, tapeworms, lungworms and bots in horses with a single dose.
Contents will treat up to 1320 lb body weight.
FOR ORAL USE IN HORSES ONLY
Net Weight: 0.225 oz (6.42 g)
NADA #141-215, Approved by FDA
Pfizer
EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
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Pfizer
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praziquantel 14.03%)
FPO: UPC

EQUIMAX™

(ivermectin 1.87%/praziquantel 14.03%)

Paste

Anthelmintic and Boticide

FOR ORAL USE IN HORSES ONLY

Removes worms and bots with a single dose.

Contents will treat up to 1320 lb body weight.

Net Weight: 0.225 oz (6.42 g)

INDICATIONS: Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism. Equimax (ivermectin/praziquantel) Paste is indicated for the treatment and control of the following parasites:

Tapeworms
Anoplocephala perfoliata

Large Strongyles (adults)
Strongylus vulgaris (also early forms in blood vessels)
S. edentatus (also tissue stages)
S. equinus
Triodontophorus spp.

Small Strongyles including those resistant to some benzimidazole class compounds (adults and fourth-stage larvae)
Cyathostomum spp.
Cylicocyclus spp.
Cylicostephanus spp.
Cylicodontophorus spp.

Pinworms (adults and fourth-stage larvae)
Oxyuris equi

Ascarids (adults and third- and fourth-stage larvae)
Parascaris equorum

Hairworms (adults)
Trichostrongylus axei

Large-mouth Stomach Worms (adults)
Habronema muscae

Bots (oral and gastric stages)
Gasterophilus spp.

Lungworms (adults and fourth-stage larvae)
Dictyocaulus arnfieldi

Intestinal Threadworms (adults)
Strongyloides westeri

Summer Sores caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae

Dermatitis caused by **Neck threadworm** microfilariae, *Onchocerca* sp.

DOSAGE AND ADMINISTRATION: This syringe contains sufficient paste to treat one 1320-lb horse at the recommended dose rate of 91 mcg ivermectin per lb (200 mcg/kg) and 0.68 mg praziquantel per lb (1.5 mg/kg) of body weight. Each weight marking on the syringe plunger delivers enough paste to treat 220 lb (100 kg) of body weight.

1. While holding plunger, turn the knurled ring on the plunger 1/4 turn to the left and slide it so the side nearest the barrel is at the prescribed weight marking.
2. Lock the ring in place by making a 1/4 turn to the right.
3. Make sure that the horse's mouth contains no feed.
4. Remove the cover from the tip of the syringe.

75-0239-X1

5. Insert the syringe tip into the horse's mouth at the space between the teeth.
6. Depress the plunger as far as it will go, depositing paste on the back of the tongue.
7. Immediately raise the horse's head for a few seconds after dosing.

Parasite Control Program: All horses should be included in a regular parasite control program with particular attention being paid to mares, foals, and yearlings. Foals should be treated initially at 4 weeks of age, and routine treatment repeated as appropriate. Consult your veterinarian for a control program to meet your specific needs. Equimax Paste effectively controls gastrointestinal nematodes, cestodes and bots of horses. Regular treatment will reduce the chances of colic caused by *Anoplocephala perfoliata* and verminous arteritis caused by *Strongylus vulgaris.*

Product Advantages: Broad-spectrum Control: Equimax Paste kills important internal parasites, including tapeworms, bots and the arterial stages of *S. vulgaris,* with a single dose. Equimax Paste contains two potent antiparasitic agents that are neither benzimidazoles nor organophosphates.

SAFETY: Equimax Paste may be used in horses 4 weeks of age and older. Stallions may be treated without adversely affecting their fertility. Safety has not been evaluated in breeding, pregnant or lactating mares.

In a tolerance study in which 3- to 4-week-old foals were treated at 10X once, loose watery stools were observed on post-treatment days 1, 2, and 5–9 in one foal. These signs resolved without treatment by day 10, and no other foals were affected.

PRECAUTIONS: The safety of Equimax Paste in mares used for breeding purposes, pregnant or lactating mares, has not been evaluated.

Equimax Paste has been formulated specifically for use in horses **only.** This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

WARNING: Do not use in horses intended for food purposes.

HUMAN WARNINGS: Not for use in humans. Keep this and all drugs out of the reach of children. Refrain from eating or smoking when handling. Wash hands after use. Avoid contact with eyes. The Material Data Safety Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Pfizer at 1-800-366-5288.

ENVIRONMENTAL WARNINGS: Ivermectin and excreted ivermectin residues may adversely affect aquatic organisms. Do not contaminate ground or surface water. Dispose of the syringe in an approved landfill or by incineration.

Store at room temperature (25°C/77°F), with excursions permitted between 15°–30°C (59°–86°F).

NOTE TO USER: Swelling and itching reactions after treatment with ivermectin paste have occurred in horses carrying heavy infections of neck threadworm (*Onchocerca* sp. microfilariae). These reactions were most likely the result of microfilariae dying in large numbers. Symptomatic treatment may be advisable. Consult your veterinarian should any such reactions occur. Healing of summer sores involving extensive tissue changes may require other appropriate therapy in conjunction with treatment with Equimax Paste. Reinfection, and measures for its prevention, should also be considered. Consult your veterinarian if the condition does not improve.

To report adverse reactions, call Pfizer Animal Health at 1-800-366-5288.

NADA #141-215, Approved by FDA

Manufactured by:
Virbac AH Inc.
3200 Meacham Blvd
Fort Worth, Texas 76137

U.S. Patent No. 5,824,653

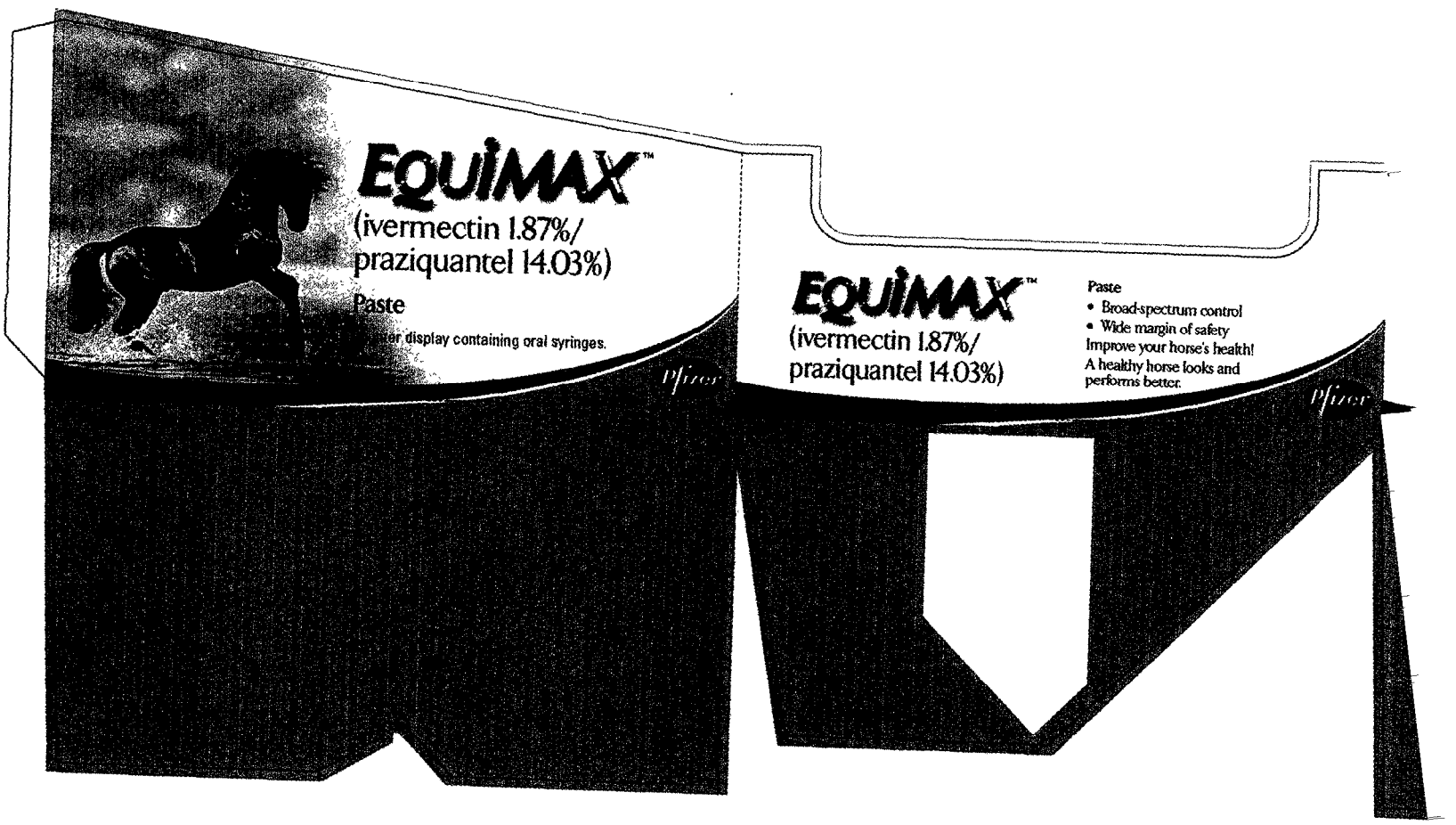
Distributed by:
Pfizer Animal Health
Exton, PA 19341, USA
Div. of Pfizer Inc
NY, NY 10017

Made in Canada
(or Made in USA)*

* Depends on site of manufacture.

Equimax is a trademark of Virbac SA.

75-0239-X1
March 2003


EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
Paste
display containing oral syringes.
Pfizer
EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
Paste
• Broad-spectrum control
• Wide margin of safety
Improve your horse's health!
A healthy horse looks and
performs better.
Pfizer

EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
Paste
Counter display containing oral syringes

pfizer

PM: UP2

EQUIMAX™
(ivermectin 1.87%/
praziquantel 14.03%)
Paste
Anthelmintic and boticide for horses
Kills important internal parasites including bots
and immature stages of *Strongylus vulgaris*.

pfizer